

REMARKS

Claims 21, 24, 26, 30, and 36-39 are pending and stand rejected. Claim 30 is objected to as dependent upon a rejected base claim, but is indicated to be allowable if rewritten in independent form. No claim is allowed. Claim 21 is amended to correct a typographical error. New claims 40-42 are added herein. Support for the new claims is provided by the specification at, e.g., paragraphs [0171], [0301]-[0306], and Examples 1-2. No new matter is added by way of the claim amendments or new claims. Entry of the claim amendments and new claims, and reconsideration in view of the following remarks are respectfully requested. Claims 21, 24, 26, 30, and 36-42 are now pending and under examination.

Rejections under 35 USC § 103(a)

Claims 21, 24, 26, and 36-39 stand rejected under 35 USC § 103(a) as allegedly obvious over Chamberlain et al. (US 2005/023083 A1) in view of Klaviniskis et al. (US 2003/014792) and Ryan (US 4,171,353). The Examiner has maintained the rejections for reasons of record. The rejections are traversed for reasons of record as well as at least the following.

In order for a combination of documents to defeat patentability, the Court in *KSR* held that the practitioner must have some reason to combine the elements in the way the claimed new invention does. *KSR International Co. v. Teleflex, Inc.*, 127 S. Ct. 1727, 1741 (2007). While the strict teaching - suggestion - motivation (TSM) test was rejected by the Court in *KSR*, clearly the decision did not hold that the Office is permitted to use the teachings of the invention itself as a guide to picking out documents that disclose elements of the invention. Applicants respectfully submit this is precisely what the Examiner has done in this case.

The Examiner has improperly disregarded claim limitations

The pending claims are directed towards pharmaceutical vaccine compositions comprising a small molecule immune potentiator (SMIP) compound of formula XXI and an antigen, where the compound of formula XXI functions as an adjuvant and is present in an amount effective to enhance the immune response to the antigen. Contrary to the characterization of the invention

made by the Examiner (*see* Office action, page 3), only claim 39 recites *a second adjuvant* as an oil-in-water emulsion; the remaining claims do not recite or require an oil-in-water emulsion.

The Examiner states that the term “vaccine” in the claim preamble as a recitation of purpose or intended use that is allegedly not entitled to patentable weight. In addition, the Examiner disregards express claim limitations that are not disclosed or suggested by the cited documents. In particular, the Examiner asserts that the claim limitations in claims 21 and 26 regarding the “amount effective to enhance the immune response in a subject to the antigen” (claim 21) and “wherein the immune response is the cellular production of one or more cytokines” (claim 26) are somehow *inherent* in the composition itself, “since a composition and its properties are inseparable.” Applicants respectfully assert that the Examiner has misapplied the rules related to the weight to be afforded to the claim preamble language and the law of inherency.

The claim preamble must be read in the context of the entire claim. “If the claim preamble, when read in the context of the entire claim, recites limitations of the claim, or, if the claim preamble is ‘necessary to give life, meaning, and vitality’ to the claim, then the claim preamble should be construed as if in the balance of the claim.” *Pitney Bowes, Inc. v. Hewlett-Packard Co.*, 182 F.3d 1298, 1305, 51 USPQ2d 1161, 1165-66 (Fed. Cir. 1999). MPEP 2111.01.

As previously pointed out by the Applicants, the claim language reciting that the compound of formula XXI is “present in an amount effective to enhance the immune response in a subject to the antigen” clearly links the body of the claim to the preamble. Accordingly, the fact that the composition is a vaccine composition should be afforded patentable weight in assessing the differences between the claimed invention as a whole and the cited documents.

With regard to the alleged inherency of the amount of compound effective to enhance the immune response, the Examiner asserts that “products of identical chemical composition can not have mutual exclusive properties” and that “any properties exhibited by or benefits from are not given any patentable weight over the prior art provided the composition is inherent. A chemical composition and its properties are inseparable. Therefore, if the prior art teaches the identical

chemical structure, the disclosed properties are necessarily present.” *See* Office action at page 4, citing *In re Spada*, 911 F.2d 705, 709 (Fed. Cir. 1990) (emphasis added).

Accompanying this response is the Declaration of Nicholas M. Valiante Pursuant to 37 C.F.R. § 1.132 (hereinafter “Valiante Declaration”). Dr. Valiante is the inventor of the present application.

The instantly claimed vaccine compositions were not known or suggested in the art prior to the discovery by the Applicants that a compound of formula XXI can function as an adjuvant and can be used to enhance an immune response to an antigen. Applicants respectfully point out that the cited documents do not teach compositions identical to the invention as claimed, which requires both an effective amount of a compound of formula XXI and an antigen. Chamberlain et al. do not disclose either the usefulness of the specified compound as a SMIP, or any composition where it is combined with an antigen. The disclosure of Chamberlain et al. appears to be disclosed solely on the direct treatment of “diseases associated with inappropriate angiogenesis.” *See* Chamberlain, paragraph [0001]. The Examiner has acknowledged that Chamberlain et al. do not disclose antigens (*see* Office Action at page 5). Thus, the “prior art composition” which the Examiner contends renders the claim limitations *inherent* is wholly hypothetical.

Contrary to the assertions of the Examiner (*see* Office action, paragraph bridging pages 4-5), this is not a case where a *known* composition has been previously used to obtain the same pharmacological effect, and the Applicants are attempting to claim the biological mechanism. As stated above, the claimed compositions (comprising a SMIP and an antigen) were not known in the prior art, nor were the compounds themselves known for use as vaccine adjuvants. The compounds of Chamberlain et al. have not been previously used to enhance an immune response to an antigen, as Chamberlain et al. do not disclose or suggest the compounds therein can be used in a vaccine composition or combined with an antigen.

“To establish inherency, the extrinsic evidence ‘must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill. Inherency, however, may not be established

by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient.' " *In re Robertson*, 169 F.3d 743, 745, 49 USPQ2d 1949, 1950-51 (Fed. Cir. 1999) (emphasis added). *See also* MPEP § 2112 (IV).

The present claims require an amount of a compound of formula XXI that is effective to enhance an immune response. The Examiner has pointed to the dosage range of 0.1 to 100 mg/kg body weight described by Chamberlain et al. as a therapeutically effective amount for the treatment of, e.g., colon and breast cancer. *See* Chamberlain et al. at paragraph [0413].

Applicants respectfully submit that the hypothetical composition suggested by the Examiner cannot properly be relied on to establish inherency. Moreover, as indicated in the Valiante Declaration, it is not possible to know whether the amount of Chamberlain's drug required to produce a therapeutic effect (such as the treatment of cancer) would be sufficient to provide an enhanced immune response to an antigen. *See* Valiante Declaration at ¶11. Accordingly, the Office has failed to establish that one of skill in the art would recognize that the express claim limitations of claims 21 and 26 recited above are necessarily present, and hence inherent, in the disclosure of Chamberlain et al. For at least this reason, the Examiner has failed to establish a *prima facie* case of obviousness.

There is no motivation to combine the cited documents

The Examiner cites *In re Kerkhoven* for the proposition that "[i]t is *prima facie* obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form third composition which is to be used for the very same purpose...the idea of combining them flows logically from their having been individually taught in the prior art. In the case at bar, appealed claims...require not more than the mixing together of two conventional spray-dried detergents." *In re Kerkhoven*, 626 F.2d 846, 850, 205 USPQ 1069, 1072 (CCPA 1980).

Kerkhoven's holding that it was *prima facie* obvious to combine different materials known to act as detergents is inapplicable to the facts of the present situation. Chamberlain et al. disclose compounds to inhibit angiogenesis, while Klaviniskis et al. disclose compositions to elicit immunological responses. Each is generally useful in principle for treating cancer, but treatment

with a therapeutic agent and vaccination / immune response development do not constitute “the very same purpose.” The Examiner has identified nothing in Chamberlain et al. indicating that its compounds or emulsions are useful for the purpose of the immunological compositions discussed in Klaviniskis et al.

The Examiner asserts that a motivation exists to combine the antigens of Klaviniskis et al. with an oil-in-water emulsion composition of Chamberlain et al. because: (1) both documents are said to disclose methods of treating breast and colon cancer, and therefore allegedly represent analogous art; (2) Chamberlain et al. is said to teach that other therapeutic agents may be employed in anticancer therapy; (3) Klaviniskis et al. is said to disclose spores which contain adjuvants that have an immunomodulatory effect and stimulate immune responsiveness; and (4) Chamberlain et al. are said to disclose oil-in-water emulsions which are allegedly known to be useful as adjuvants that provide slow release of an antigen (as evidenced by Ryan).

Applicants respectfully submit that the Examiner’s rationale for combining Chamberlain et al. and Klaviniskis et al. relies on mischaracterization the cited documents.

Klaviniskis et al. appear to have arrived empirically at satisfactory vaccine compositions comprising *B. subtilis* spores as an adjuvant and optionally an antigen (see Klaviniskis et al. at Abstract). There is no suggestion by Klaviniskis et al. that any improvement is needed or that there is any problem to be solved by altering the disclosed compositions. Klaviniskis et al. simply teach that certain specific compositions having significantly different chemical properties from those required by the instant claims were useful as vaccines. Thus, as a preliminary matter, Klaviniskis et al. provide no incentive to look to any other document for improvements, nor do Klaviniskis et al. provide any guidance as to what modifications should be made to the vaccine composition to effect any improvement.

Assuming solely for the sake of argument, however, that a practitioner might seek to improve the vaccine compositions disclosed by Klaviniskis et al., there are a myriad number of possible modifications one of skill in the art could have made, in particular in view of the Examiner’s apparent position that any disclosure related to methods of treating breast or colon

cancer is considered to be analogous art. The Examiner has not provided a sufficient rationale to explain why, in view of the acknowledged limitations of the cited documents and the numerous alternatives available, one of skill in the art would have been motivated to modify the disclosure of Klaviniskis et al. in the particular way proposed by the Examiner to arrive at the claimed vaccine compositions.

The Applicants note that the discovery that *B. subtilis* spores can function as an adjuvant and stimulate an immune response is the key feature of Klaviniskis' invention. Applicants respectfully assert that the Examiner has not provided a sufficient rationale to explain why one of skill in the art would have been motivated to combine the disclosure of Klaviniskis et al. with the compounds of Chamberlain et al., which had no known immunogenic properties, let alone to combine these references into a single composition in the way that the claimed invention does.

The Examiner's alleged motivation to combine relies in part on the disclosure of oil-in-water emulsions in Chamberlain et al., which the Examiner states are known to be useful as adjuvants that provide slow release of the antigen, as allegedly evidenced by Ryan et al. Applicants respectfully submit that this statement mischaracterizes the disclosures of Chamberlain et al. and Ryan.

Contrary to the Examiner's position, the 'oil-in-water' emulsions of Chamberlain et al. specifically relate to emulsions for oral administration. *See* Chamberlain et al. at paragraph [0394] ("Pharmaceutical formulations adapted for oral administration may be presented as discrete units such as ...oil-in-water liquid emulsions.") Chamberlain et al. do not disclose or suggest that their formulations are useful as adjuvants, and no rationale or evidence has been provided to show that such emulsions would necessarily have the properties of an adjuvant.

As evidenced by the Valiante Declaration, it is well known in the art that vaccine compositions require specialized formulations and are not ordinarily combined with small molecule therapeutic agents. *See* Valiante Declaration at ¶8. In addition, one of skill in the art would recognize that oil-in-water formulations of small molecule drugs are not necessarily suitable for use as vaccine formulations. *See* Valiante Declaration at ¶5. Thus, the skilled artisan would not have

inferred that the oral oil-in-water emulsions described by Chamberlain et al. would be useful as vaccine adjuvants.

In addition, the Examiner's reliance on Ryan appears to be misplaced. The disclosure by Ryan that certain oil-in-water emulsion-type adjuvants are known would not logically lead one of skill in the art to conclude that *any* oil-in-water emulsion comprising a compound of *any* chemical structure could be used as a vaccine adjuvant. In addition, Ryan expressly teaches away from oral administration of peptide antigens with oil-in-water emulsions, which is the combination that the Examiner seems to rely upon for the rejection. Clear teaching away in the art rebuts a *prima facie* case for obviousness, because it demonstrates that one of ordinary skill would not have expected this combination as claimed to work.

In the absence of any other suggestion or guidance to suggest that the compounds have such activity, there is simply no basis to suggest that one of skill in the art would have expected Chamberlain's oil-in-water emulsions to function as adjuvants or to provide an enhanced immune response to an antigen, as in Klaviniskis et al. Accordingly, the Examiner's reliance on the disclosure of oral oil-in-water emulsions by Chamberlain et al. as allegedly providing a motivation to combine the reference with Klaviniskis et al. is improper.

The Examiner further contends that the discussion of combination therapy in Chamberlain et al. provides a motivation to combine Chamberlain's compounds with the antigens of Klaviniskis et al. Applicants respectfully disagree. Chamberlain et al. discuss combination therapies comprising administration of a described compound with another chemotherapeutic, hormonal, or antibody agent at paragraph [0414].

Applicants respectfully submit that none of the agents contemplated by Chamberlain et al. is an immunological composition, and none would be expected to work by eliciting an immune response. Accordingly, one of skill in the art would have no reason to combine the compounds of Chamberlain et al. with any antigen or to include them in a vaccine-like composition. *See* Valiante Declaration at ¶5.

Chamberlain et al. disclose compounds with therapeutic uses, but no connection with immunological compositions. Even if the compositions of Klaviniskis et al. were to be used with the compounds from Chamberlain et al. in the treatment of a single patient, that does not establish a *prima facie* basis for combining those materials into a single composition, as claimed.

The Examiner's analysis relies heavily upon the supposition that one of ordinary skill would have been motivated to mix a therapeutic agent taught in Chamberlain et al. with an immunogenic composition of Klavinskis et al. Applicants respectfully assert that the combination of these two references is improper in the absence of a reason for Chamberlain's compounds to be physically combined with a vaccine composition or admixed with an antigen.

The Examiner has not provided evidence that a person of ordinary skill would routinely combine a vaccine with a therapeutic agent, and overlooks the many reasons why one of skill in the art would not physically combine such agents. It is well known that the formulation of drugs and the determination of their mode of administration and dosing schedules must take into account many factors including drug toxicities, tolerability, efficacy, and bioavailability. Just because two drugs could both be used in methods to treat a common disorder does not provide motivation to combine the two in a single composition, in view of the expected differences in dosages, frequency and timing, route of administration, dietary effects, etc.

As evidenced by the Valiante Declaration, it is well known in the art that vaccine compositions are not ordinarily combined with small molecule therapeutic agents. *See* Valiante Declaration at ¶8. Moreover, practitioners of this art would recognize that mixing an immunogenic composition and a therapeutic agent into a single composition would limit the ability to optimize the frequency and route of administration for each agent. *See* Valiante Declaration at ¶8. In addition, one of skill in the art would recognize that mixing these agents could lead to adverse drug interactions, for example, by eliciting an immune reaction to a drug physically admixed with the vaccine composition. *See* Valiante Declaration at ¶9. For at least these reasons, a skilled practitioner in this art would not combine a vaccine and a small molecule drug like into a single composition merely so they can be administered as a single composition. *See* Valiante Declaration at ¶9.

As previously pointed out by the Applicants, concurrent treatment with a vaccine and another therapeutic agent does not require mixing these materials together. In view of the expected differences in routes and schedules of administration and the potential for adverse interactions, a person of skill in the art ordinarily would *not* mix such agents together. *See* Valiante Declaration at ¶10. Where concurrent treatment is desired, a skilled practitioner would preferably administer each agent to a single patient *separately*, allowing vaccine and small molecule agents to be delivered under optimal conditions and reducing the likelihood of adverse interactions. *See* Valiante Declaration at ¶10.

There is no reasonable expectation of success

As discussed herein, Chamberlain et al. neither teach nor otherwise suggest that the disclosed compounds can function as adjuvants or enhance an immune response. The teachings of Ryan regarding known oil-in-water emulsion adjuvants cannot fairly be said to teach that *any* oil-in-water emulsion is useful as an adjuvant, and thus do not provide the skilled practitioner with a reasonable expectation that the emulsions disclosed by Chamberlain et al. will function as an adjuvant, in the absence of any additional reason to expect such activity. In addition, none of the additional agents contemplated by Chamberlain et al. for use in conjunction with the disclosed compounds would be expected to function by eliciting an immune response. The Examiner has provided no explanation why one of skill in the art would reasonably believe such agents could be successfully replaced by an antigen or immunogenic composition in a hypothetical combination. Accordingly, one of skill in the art would have no reason to combine Chamberlain's compounds with an antigen or immunogenic composition (*see* Valiante Declaration at ¶5).

In view of the foregoing remarks, the Applicants respectfully submit that one of skill in the art would not have had a reasonable expectation that Chamberlain's compounds would be useful in combination with an antigen or an immunogenic composition to prepare a vaccine composition providing an enhanced immune response to an antigen.

Objective evidence of nonobviousness

Even if a *prima facie* case of obviousness were established, which the Applicants do not concede, it can be overcome by objective evidence of nonobviousness. The composition proposed by the Examiner comprising a compound of Chamberlain et al. with an immunological composition from Klaviniskis, relies in part upon the ‘oil-in-water’ emulsions in Chamberlain, or the spores mentioned as adjuvants in Klaviniskis, to elicit an adequate immune response to the antigen.

The compounds of formula XXI produce an unexpected immune-stimulating response or agonistic effect to an antigen in the claimed compositions. *See* Valiante Declaration at ¶12. These compounds enhance the immune response elicited by an antigen, an effect which was not disclosed or suggested in the prior art. As evidenced by the Valiante Declaration, these effects could not have been expected from the cited documents, which disclose only antiangiogenic or antagonistic activity for the compounds of Chamberlain et al. *See* Valiante Declaration at ¶12. Thus, the compositions as claimed would not have been expected to provide an enhanced immune response to an antigen without the addition of an adjuvant. The discovery that the claimed compositions are unexpectedly effective without an adjuvant overcomes any alleged basis for an obviousness rejection.

CONCLUSION

In view of the above, each of the presently pending claims in this application is believed to be in immediate condition for allowance. Accordingly, the Examiner is respectfully requested to withdraw the outstanding rejection of the claims and to pass this application to issue. If it is determined that a telephone conference would expedite the prosecution of this application, the Examiner is invited to telephone the undersigned at the number given below.

In the event the U.S. Patent and Trademark office determines that an extension and/or other relief is required, applicant petitions for any required relief including extensions of time and authorizes the Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to Deposit Account No. 03-1952 referencing docket no.223002107200. However, the Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

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Respectfully submitted,

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